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PANEL DISCUSSION — LUNG CANCER SCREENING: DIAGNOSTIC ALGORITHMS

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Contrast enhanced CT and PET in lung cancer screening

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Abstract

This paper aims to discuss the role and the accuracy of positron emission tomography (PET) and to evaluate computed tomography (CT) contrast enhancement in diagnosing the nature of lung nodules detected by low-dose CT, performed as screening for lung cancer. When applying strict admission criteria to the test, CT contrast enhancement is feasible in 40% of nodules and gives an accurate diagnosis of benignity when enhancement is $<$15 HU: this occurs in only 5% of cases, but the diagnosis has to be considered certain, sparing further examination and/or follow-up. PET, performed with the most up-to-date equipment, can evaluate nodules with diameter $>$7 mm. The sensitivity is 87% and specificity 76%. Contrast enhancement study and PET are promising in the diagnostic work-up of lung nodules, as they reduce follow-up, the number of Fine Needle Aspiration Biopsy (FNAB), costs, radiation exposure and patients' anxiety.

Keywords: *Diagnostic imaging; lung cancer (diagnosis); computed tomography; X-rays; contrast medium; positron emission tomography.*

Introduction

Low-dose spiral computed tomography (ld-CT) of the chest has proved effective in detecting early stage lung cancer in high-risk individuals. Nonetheless, a high prevalence of benign pulmonary nodules and tissue diagnosis are critical factors before considering large-scale screening programs. The diagnosis of detected nodules is generally delivered by repeating CT, to evaluate the growth rate: for this purpose thin-slice CT (ts-CT) has to be applied to a high proportion of subjects, with a complex algorithm of 3D reconstruction for minimal growth assessment, with a diagnostic period extending up to 2 years. The doubling time of lung cancer may vary from 20 to 400 days[1] and this wide range complicates the diagnosis. Nevertheless the delay in diagnosis caused by the need for a long follow-up occurs in slow-growing tumors and thus does not affect early diagnosis, but causes a rise in costs, X-ray exposure and the patient's anxiety.

To minimize the diagnostic work-up and to reduce the time to reach diagnosis, computed tomography (CT) contrast enhancement and positron emission tomography (PET) can be used to guide the diagnosis with different degrees of accuracy, according to the characteristics of the nodule and test results.

Methods

Contrast enhancement

A careful selection of nodules susceptible for the test is mandatory to obtain reliable results. The nodule to be examined has to be solid and homogeneous on pre-contrast thin-section CT images. Nodules containing fat or calcifications have to be excluded. No CT artifacts, such as cardiac motion or beam attenuation by adjacent dense structures, should be present in the sections.

The CT technique has to be standardized: the standardization proposed by Swensen[2] is universally accepted and few changes to the protocol are suggested. Patients are examined with 1 mm collimation if the

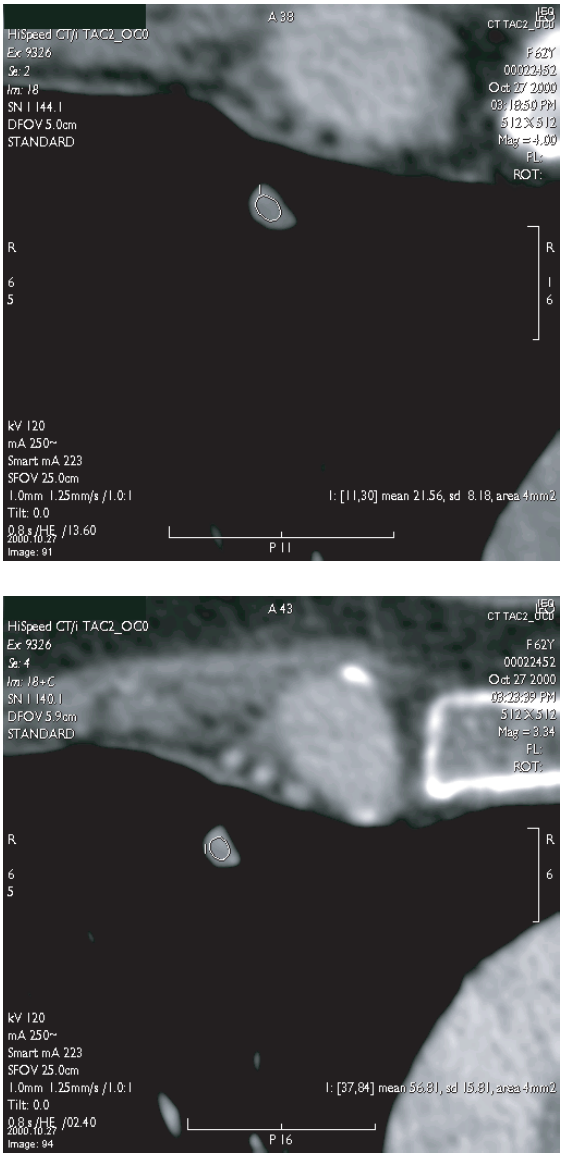

Figure 1 **The mean density of a 6 mm solid lung nodule at pre-contrast CT scan was 21.56 ± 8 HU. One minute after i.v. injection of iodated contrast medium the density value was 56.8 ± 15 HU. Enhancement of 35.3 HU was considered highly suspicious for malignancy and led to a surgical biopsy, followed by lobectomy, demonstrating a T1N0 adenocarcinoma.**

Table 1 Results obtained by CT contrast enhancement in 60 nodules

	≤ 10 HU	11–29 HU	≥ 30 HU
Benign	3	26	10
Malignant		2	19

Diagnosis was obtained by pathology in all malignant cases and by 3-year follow-up in benign cases.

nodule diameter is 5–10 mm and with 3 mm collimation if the nodule is >10 mm. CT scans of the region of interest (ROI) are performed 30, 60, 120, 180 and 300 s after the i.v. injection of 2 ml/kg of non-ionic iodated contrast medium (300–350 mg/ml) at 2 ml/s. Nodular density is measured using the same circular or elliptic ROI on the same slice of the nodule, identified manually by its shape and surrounding structures (bronchi and/or vessels). Enhancement is expressed as the difference between basal HU and maximum HU measured after contrast injection.

PET scan

Spatial resolution is the main limitation to the use of fluorine-18-labeled fluorodeoxyglucose (^{18}F-FDG) PET scan for characterizing pulmonary nodules. The choice of the minimum diameter of nodules susceptible to a PET scan with a sufficient degree of confidence in a negative result depends on the type of the available PET or CT-PET scanner. The latest equipment is described as reliable down to 7 mm.

Personal series

We report the results obtained in 138 subjects with a lung nodule >5 mm in diameter diagnosed by ld-CT performed annually (between June 2000 and June 2003) in a cohort of 1035 volunteers enrolled in a pilot study for early diagnosis of lung cancer[3]. They were evaluated for eligibility and were submitted to CT contrast enhancement when the density was measurable and > 0 HU with SD <20% of the value, and to PET when the diameter was > 7 mm.

CT contrast enhancement study was performed on a Hispeed Advantage or a 16 slices Lightspeed General Electric (GE Medical System, Milwaukee, US). PET scans were performed on a GE Advance (GE Medical System, Milwaukee, US) with 55 cm transaxial and 15.2 cm axial fields and 4.25 mm collimation 60 min after i.v. injection of 3.7 MBq/kg of ^{18}F-FDG. Images were normalized by pixel by pixel activity, administered dose and the patient's weight.

Results

The mean unenhanced density of nodules was considered measurable in 61/138 (44.2%) cases and was ≤0 HU in 19 nodules, eventually diagnosed as benign: diagnosis was confirmed by 3-year follow-up. Contrast enhancement was feasible in 60 nodules (44 solid and 16 partially solid) and resulted in values of ≤10 HU in three cases, eventually diagnosed as benign, and ≥30 HU in 29 cases, among which 19 were malignant (Fig. 1). Values were indeterminate in 28 nodules, ranging between 11 and 29 HU, among which two were later diagnosed as malignant (Table 1).

^{18}F-FDG-PET was performed in 55 of the 138 subjects (39.8%) having a nodule >7 mm in diameter: 32 had

positive PET with 26 diagnosed as having a tumor, while six subjects with positive PET were biopsied for inflammatory bronchiectasis, inflammatory intraparenchymal node, pulmonary fibrosis with lymphocytic reaction (Fig. 2), inflammatory pseudotumor associated with bronchiolitis, obliterans-organizing pneumonia and tuberculosis (TBC). Among the 23 subjects with negative PET, there were four tumors diagnosed at 3 months of follow-up CT: two adenocarcinomas (7.3 and 8.5 m in diameter), one carcinoid (18 mm in diameter) and one 18 mm bronchoalveolar carcinoma.

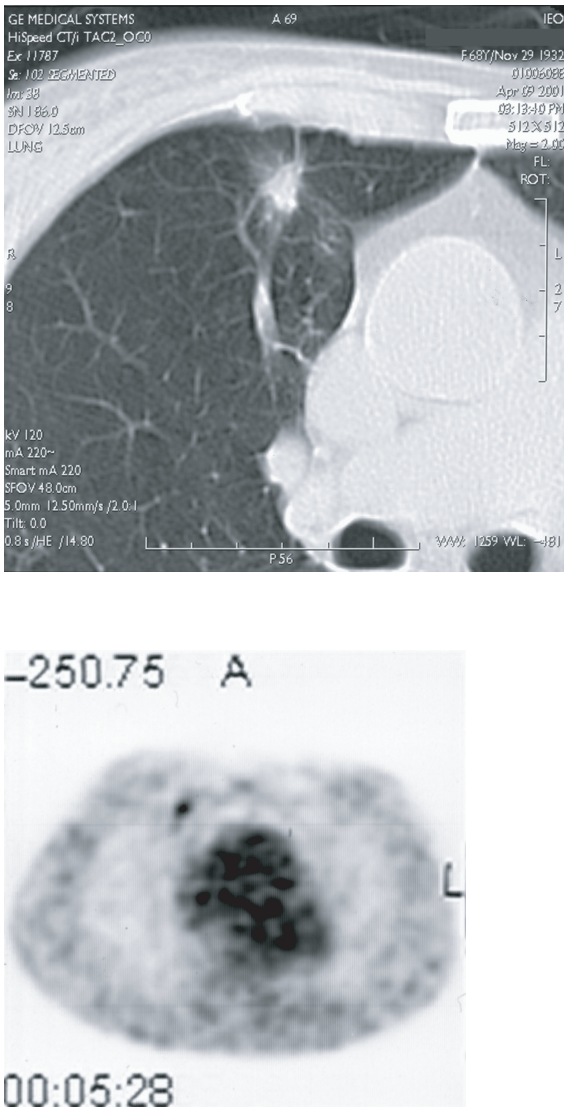

Figure 2 **A 12 mm solid nodule with suspicious CT appearance, but negative at contrast enhancement study, was PET positive. Surgical biopsy revealed pulmonary fibrosis with lymphocytic reaction.**

Discussion

A major concern with systematic use of spiral CT for early diagnosis of lung cancer in a high-risk population is the frequent occurrence of false-positive findings in benign nodules. In the first Mayo Clinic report using multi-slice CT, 69% of 1520 screened volunteers had uncalcified pulmonary nodules, but only 3% proved to be malignant. Differential diagnosis of such nodules is often difficult and greatly increases the probability of unnecessary investigations, the total cost of the screening program and patients' anxiety.

Table 2 ***Subjects eligible for diagnostic work-up by CT contrast enhancement and PET and diagnosis obtained by the tests***

	ts-CT	CT contrast enhancement	PET
Subjects examined	138	60 (43.5%)	55 (39.9%)
Diagnosed benign	6 (4.3%)	3 (5%)	23 (41.8%)
Diagnosed malignant		29 (48.3%)	32 (58.2%)
Indeterminate	132 (95.6%)	28 (46.6%)	

Table 3 ***Sensitivity, specificity, and positive and negative predictive values (PPV and NPV) of CT contrast enhancement (cut-off at 10 HU) and PET***

	CT contrast enhancement (%)	PET
Sensitivity	100	86.7% [0.69–0.96]
Specificity	23	76% [0.55–0.90]
PPV	65.5	81.2% [0.63–0.93]
NPV	100	82.6% [0.61–0.95]

Contrast enhancement of pulmonary nodules evaluated by CT is well known by radiologists but poorly accepted by clinicians. The careful selection (Table 2) of appropriate cases to be submitted to the test and the use of a cautious cut-off value (10 or 15 HU) to define benign or suspicious nodules led to a high percentage of sensitivity (Table 3), thereby excluding cases from a long follow-up. When applying these protocols, the number of cases that can be evaluated is reduced to 40% of detected nodules, and the number of diagnoses of benign disease is really low, i.e. 5%, but they can be considered definite diagnoses.

A recent meta-analysis has highlighted the diagnostic value of PET in undetermined pulmonary nodules[4]. The majority of lung cancers retain ^{18}F-FDG because of their high metabolic rates: PET can characterize the nature of pulmonary nodules because of the ability of the technique to demonstrate hypermetabolic foci. Benign pulmonary lesions, such as adenomas, hamartomas and inflammatory nodules, do not retain ^{18}F-FDG to the same extent as malignant tumors. However, in some instances, PET scans produce false-positive results, for instance in active cellular or granulomatous inflammation, or false-negative scans, as in some cases of well-differentiated

adenocarcinomas, bronchoalveolar cell carcinomas and carcinoid tumors.

Contrast enhancement study and PET are promising in diagnostic work-up, and they reduce the number of high-risk FNAB in heavy smokers.

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Lung cancer screening: measurement and follow-up intervals

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Abstract

Detection of growth is a practical non-invasive method to classify the common small pulmonary nodules detected at thin-section (multislice) computed tomography (CT). This paper describes accuracy and appropriate follow-up intervals for different methods of growth detection at CT: visual analysis, two-dimensional measurement, three-dimensional computer-aided volumetry.

Keywords: *Volumetry; computer-aided diagnosis; segmentation; growth detection.*

Introduction

Early peripheral lung cancer most often presents as a small non-calcified pulmonary nodule. However, as most small pulmonary nodules demonstrated at screening computed tomography (CT) are benign non-invasive diagnostic algorithms are required for differentiation between benign and malignant lesions [1–4].

The most promising concept suggests performing invasive procedures only in nodules larger than a certain size threshold (e.g. 10 mm) at the initial examination and following all other nodules with thin-section low-dose CT. Nodules which resolve or decrease in size can be considered benign, nodules which do not grow need to be followed to exclude slow growth and invasive procedures are only performed in growing nodules. However, as demonstration of growth requires a certain time interval between baseline and the follow-up scans, there is an inherent risk of dissemination of malignancy in the interval. Therefore, the interval required for correct classification should be as short as possible.

Growth rate

The growth rate of pulmonary nodules of different etiology has been studied extensively for many years. Doubling times (time required for doubling of the tumor volume) of malignant nodules range from 11 to 465 days [5]. Lesions with doubling times beyond this range are most likely benign with faster doubling times representing focal inflammatory nodules and slower doubling times representing chondrohamartoma, intrapulmonary lymph node or granuloma.

Assuming even growth in a spherical lesion doubling of volume is represented by an increase in diameter of 26%, e.g. from 4 to 5 mm or from 20 to 25 mm.

Measurement techniques

Evaluation for possible growth of pulmonary nodules can be performed by visual comparison of baseline and follow-up scans. This is appropriate when marked differences in diameter are present. It is, however, not reliable for detection of subtle growth.

Two-dimensional measurement of the largest nodule diameter with or without analysis of a second diameter, usually perpendicular to the largest diameter, is more precise. Assessment of the nodule diameter in the patient's longitudinal axis (*z*-axis) is limited by the slice thickness due to partial volume effects: the smaller the slice thickness the more precise the measurement. Only isotropic voxels using submillimeter slice thickness in thin-section CT measurement of the *z*-axis diameter is as precise as the axial diameter.

The most recent development in growth detection is three-dimensional volumetry of thin-section (multislice) CT data[6].

The technique is based on computerized segmentation to isolate the nodule from adjacent vessels, mediastinum or chest wall. By identification of all voxels comprising the nodule the volume is calculated and can be given in mm^3 (Fig. 1).

Theoretically, this approach should allow detection of growth even in lobulated or spiculated nodules in which the maximum diameters do not increase but the volume increases by filling in of areas between spicules.

Obviously, for application of this technique in clinical practice the precision (agreement between true and measured volumes) and even more importantly the reproducibility (agreement between two measurements of the same nodule) need to be known.

Volumetry tools of different manufacturers have been tested on artificial nodules in phantoms with and without deformation of the nodule shape maintaining the nodule volume between the two measurements. These have shown a high reproducibility with measurement errors of $<3\%$[7]. As phantom studies cannot simulate in vivo conditions (motion artifacts from cardiac pulsation, respiration and patient movement) these results can not be automatically transferred into clinical routine. Patient studies of subjects with pulmonary metastases were also performed showing higher measurement errors particularly in ill-defined nodules or lesions adjacent to vessels or pleura whereas reproducibility was better in well defined nodules surrounded by aerated lung[8]. When interpreting results of the clinical studies one has to consider whether repeat measurements were performed on the same CT dataset or on different CT scans. Ideally, these should be obtained within a short interval to avoid changes in nodule volume between the two measurements, however, they should also be obtained at separate settings including patient positioning, scout view and breath hold to simulate comparison of baseline and follow-up CT scans.

The technique can be applied to clinical cases only if the reproducibility of computer-aided volumetry in a certain type of nodule is known for the tool used.

Follow-up interval

The appropriate follow-up interval for detection of growth directly depends on the precision of measurement and the expected doubling time of growing nodules. If, for example, the measurement error of a given volumetry tool is less than 50% and the doubling time is 400 days—representative of slow-growing non-small cell lung cancer—follow-up before 200 days will not predict growth correctly.

If, on the other hand, the measurement error is less than 5% and the doubling time is only 30 days—representative of rapidly-growing small cell cancer—growth can be diagnosed within 2 days. Also, the baseline volume of a given nodule has to be taken into account as the precision (or error) of measurement depends on the ratio of the nodule diameter and the voxel size: precision will be lower in smaller nodules. For practical purposes with the known range of doubling times in lung cancer follow-up intervals for visual assessment or two-dimensional measurement of 3 months appear useful.

If a sophisticated technique is used growth may be demonstrated in malignant nodules within 30 days[9]. If very precise and robust volumetry tools become available, very early follow-up after only 1 or 2 weeks may allow correct classification of even small pulmonary nodules, thus decreasing the risk of tumor spread in the follow-up interval.

Pitfalls

Obviously, there is no threshold to allow differentiation between benign and malignant nodules in all cases. Therefore, even precise detection of volume change in a given interval does not automatically predict the nature of a nodule.

Conclusion

Visual analysis or two-dimensional measurement of pulmonary nodules as currently used requires follow-up for many months or even years for detection of slow growth in malignant nodules. Modern three-dimensional volumetry tools promise much higher precision and have the potential to detect growth even in slow-growing tumors within a few weeks or even days. For application of these tools in clinical practice, however, their precision (or measurement error) needs to be analyzed in order to

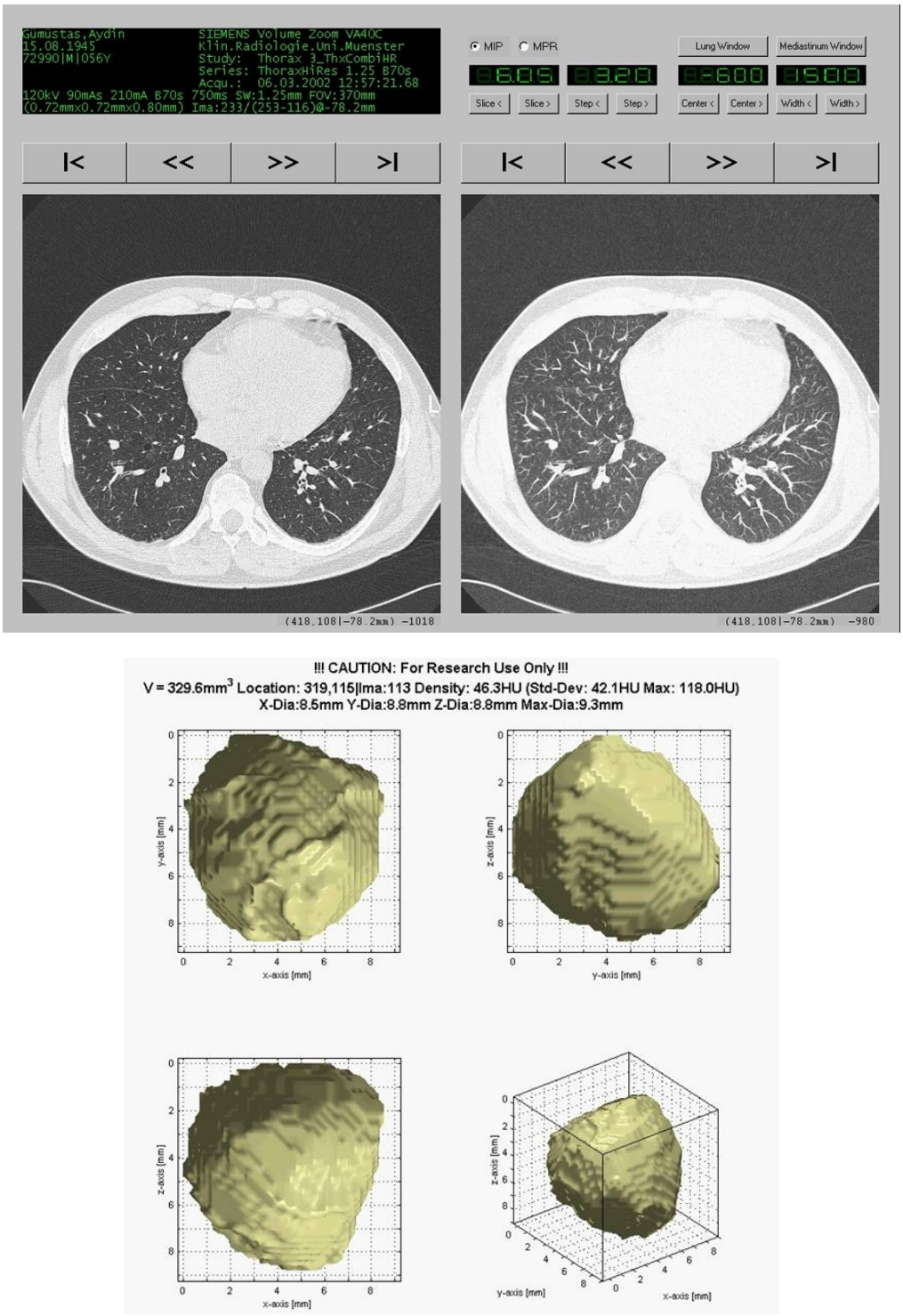

Figure 1 **Example of computer-assisted volumetry at low-dose CT (prototype Lung care™ software, Siemens Corporation, Erlangen, Germany). (a) Thin-section image (left) and thin-section sliding maximum intensity projection (right) at the level of the inferior pulmonary veins showing a central pulmonary nodule in the right lower lobe. (b) Segmented nodule with indication of diameters, volume and density of nodule.**

define appropriate follow-up intervals. Also, the size and expected doubling time of nodules have to be taken into account.

Key points

- Detection of growth and calculation of doubling times allows differentiation between benign and malignant pulmonary nodules.
- Computer-assisted three-dimensional (volumetric) measurement is superior to visual assessment or two-dimensional measurement.
- Computer-aided volumetry tools are commercially available.
- Precision and reproducibility of volumetry tools differ and need to be analyzed individually before clinical use.

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